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COMMENTARY: A Window of Opportunity: The Diagnosis of Gonadotropin Deficiency in the Male Infant*

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A common cause of micropenis is congenital hypogonadotropic hypogonadism, whether isolated or associated with multiple pituitary hormone deficiencies. The postnatal surge in FSH, LH, and testosterone in the male infant as a consequence of the continued function of the fetal GnRH pulse generator provides a 6-month window of opportunity to establish the diagnosis of hypogonadotropic hypogonadism and alert the clinician to the possibility of its association with multiple pituitary hormone deficiencies. When ACTH or GH deficiency or both deficiencies are present, hypoglycemia and cortisol deficiency can lead to neonatal and infantile death or increased morbidity. Establishing the diagnosis of hypogonadotropic hypogonadism in infancy preempts the uncertainties and delays in distinguishing constitutional delay in puberty from hypogonadotropic hypogonadism. Accordingly, hormone replacement therapy can be initiated at the normal age of pubertal onset.

The ontogenesis of infantile testicular function, including the possible significance of the infantile surge in gonadotropins and testosterone, is reviewed. The molecular basis for certain developmental disorders associated with hypogonadotropic hypogonadism and micropenis is considered and the management and treatment of congenital hypopituitarism discussed. (*J Clin Endocrinol Metab* 90: 3122–3127, 2005)

IN RECENT YEARS remarkable advances have occurred in the following areas:

1) In our knowledge of the complex developmental endocrinology and neuroendocrinology of the fetus and infant.

2) In new technology that has yielded dramatic advances in imaging techniques and new diagnostic modalities including more sensitive, specific immunoassays for gonadotropin, sex steroids, anti-Müllerian hormone/Müllerian inhibitory substance (AMH/MIS), and inhibin B (and A).

3) In the clinical diagnosis of isolated hypogonadotropic hypogonadism (IHH) including the recognition of its phenotypic and etiologic heterogeneity.

4) Continued progress in establishing a specific genetic etiology and molecular pathogenesis for this heterogeneous syndrome, IHH, and neonatal multiple pituitary hormone deficiencies, including critical insights gained from mouse models (targeted mutagenesis, expression of transgenes).

In childhood, FSH, LH, and sex steroid secretion, although present, are low. However, in boys there is a window of opportunity from birth to about 6 months of age (and in girls to ~2 yr of age) to establish the diagnosis of hypogonadotropic hypogonadism (reviewed in Refs. 1, 2).

In the human being, the fetal hypothalamic GnRH pulse generator has developed and is well functional by the end of the first trimester.

- In childhood FSH, LH, and sex steroid secretion are low.
- Plasma FSH and LH low in umbilical cord blood (inhibitory effect of high circulating placental derived estrogens on hypothalamus and pituitary gonadotropes).
  BUT
- In the male infant: serum FSH, LH, and testosterone levels increase during second week, reach a maximum at 4–10 wks, and decline by about age 6 months to low levels.
- In the female infant: increase in serum FSH and LH (and inconstantly E2) for 2–3 yrs.

Striking features of the ontogeny of the GnRH pulse generator (3) are: 1) its development and function in the fetus and the continued function of the oscillator in infancy, the developmental phase; 2) the gradual dampening of its activity during late infancy (earlier in boys than girls) leading to its virtual but not absolute quiescence during childhood and as a consequence the low secretion of FSH and LH by the pituitary gland and sex steroids by the gonads, the prepubertal juvenile pause; 3) the gradual disinhibition and reactivation of the GnRH pulse generator mainly at night during late childhood leading to the increased amplitude of the GnRH pulses, which are reflected in the progressively increased and changing pattern of circulating LH pulses with the approach of and during puberty, the pubertal phase, including the augmented plasma LH response to iv GnRH administration; and finally 4) the attainment of the adult or fully mature phase.

In both the male and female, the concentration of plasma FSH and LH is low in umbilical cord blood owing to the

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Abbreviations: AMH, Anti-Müllerian hormone; GPR54, G protein-coupled receptor 54; IHH, isolated hypogonadotropic hypogonadism; hCG, human chorionic gonadotropin; KAL, Kallmann syndrome; LHX3, LIM class of homeodomain protein-3; MIS, Müllerian inhibitory substance; PRL, prolactin; PROP1, Prophet of Pit-1.

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inhibitory effect of the high circulating levels of placenta-derived estrogens on both the GnRH pulse generator and pituitary gonadotropes (3–5). Within a few minutes after birth, in the male neonate, a brief surge in LH secretion (about 10-fold greater concentration than in cord blood) is followed by an increase in the serum concentration of testosterone, which persists for about 12 h (6, 7). In the female neonate, this increase in LH does not occur. FSH levels during the first neonatal days are low in both sexes. After the fall in circulating placentally derived steroids (especially estrogens) during the first few days after birth, the subsequent disinhibition of the neonatal GnRH pulse generator-pituitary gonadotropin apparatus leads to reactivation of the sex steroid inhibited pituitary gonadotropin-gonadal system at 1–2 wk of age (8); the increase in FSH and LH secretion evokes increased secretion of gonadal sex steroids (9).

This transient surge in the hypothalamic GnRH pulse generator-pituitary gonadotropin-gonadal apparatus, sometimes called the minipuberty of early infancy, is associated with a pubertal concentration of circulating LH (higher in the male) and FSH (higher in the female) in the male and female infant, but the amplitude and duration of this reactivation differ in the two sexes (see bulleted list on previous page). In the male infant, serum FSH and LH levels increase during the second postnatal week, reach a maximum at 4–10 wk and decline by about age 6 months to the low levels that are present until the onset of puberty. In the female, the increase in FSH and LH (and inconstantly estradiol) persists for 2–3 yr, but the values are highly variable and inconstant (10).

In the male infant, the concentration of serum testosterone follows the pattern of LH secretion, reaching a peak at about 3 months of age with a subsequent decline to prepubertal values by 6–9 months of age (3, 9, 10). Soon after birth Leydig cell numbers increase to reach a peak at about 3 months of age, followed by striking regression and apoptosis of the fetal (and infantile) Leydig cell (11–13). Inhibin B, a glycoprotein member of TGFβ superfamily, is secreted by the Sertoli cells in prepubertal boys; it is an indicator of Sertoli cell function (but in prepubertal boys not germ cell function or number) and an important regulator of FSH secretion. Present in cord blood, circulating inhibin B increases soon after birth and reaching a peak at 4–12 months of age (to greater values than in the adult male), decreasing to a nadir from 3 to 9 yr of age and increasing again with the onset of puberty (10). Its profile reflects the continued wave of Sertoli cell proliferation (which begins in the fetus) during infancy, which continues at a low level during the juvenile pause and increases again with the onset of puberty and persists until late puberty when terminal differentiation of Sertoli cells occur (14). In hypogonadotropic hypogonadism, the plasma concentration of inhibin B remains low (15, 16).

AMH/MIS, the earliest Sertoli cell hormone secretion in the human fetus and like the inhibins, a glycoprotein member of the TGFβ family, is present in cord blood from males but not females, rises rapidly in concentration in boys during the first month, reaching a peak level at about 6 months of age, and then slowly declines during childhood, falling to low levels in puberty (17, 18); the latter related to increased testosterone secretion. Its secretion is mainly constitutive.

Both inhibin B and AMH/MIS assays are useful for determining the presence and function of Sertoli cells in male infants and prepubertal boys. They replace the human chorionic gonadotropin (hCG) stimulation test in the group of initial laboratory tests used as a marker for the presence of testes in bilateral cryptorchidism. [In the rare persistent müllerian duct syndrome due to a mutation in the gene encoding AMH, AMH levels (but not inhibin B) are low despite intact testes.]

In sum, the neonatal-midinfancy surge in pulsatile gonadotropin secretion is attributable to an increase in GnRH pulse amplitude and is associated with the following:

- Increase in testicular volume (by direct measurement) due to increase in seminiferous tubule length (~6-fold increase in yr 1) (13, 19).
- Rapid expansion of Sertoli cell population (makes up ~85–95% of seminiferous tubular cell mass) (14).
- High concentration of circulating inhibin B (low in hypogonadotropic hypogonadism).
- Sertoli cell number, including postnatal proliferation, is a determinant of spermatogenic function (reviewed in Ref. 20).
- The total number of germ cells increases up to about 100 d (21), indicating mitotic activity [and the transformation of gonocytes into Ad (dark) spermatogonia (the stem cell for spermatogenesis] and subsequently decreases mainly by apoptosis (22).

The suggestion is that the transient postnatal to midinfancy function of the GnRH pulse generator in the male infant is related to future spermatogenic function and fertility (20, 23, 24). The postnatal surge apparently is not essential for masculine-typical psychosexual development (25); the brain in congenital hypogonadotropic hypogonadism including Kallmann syndrome is masculinized by testosterone therapy at puberty despite the lack of an infantile surge in gonadotropins and testosterone. Of interest, an LH and testosterone surge is absent in the complete androgen insensitivity syndrome (26, 27). Parenthetically, in the McCune-Albright syndrome, an activating mutation in the Gsα gene primarily expressed in the Sertoli cell can cause macroorchidism due to Sertoli cell proliferation and hyperfunction with increased concentration of serum inhibin B and AMH but without increased testosterone levels due to Leydig cell hyperplasia, elevated gonadotropins, or signs of puberty (28).

Clinical Aspects

A cardinal feature of IHH is the presence of a micropenis with or without associated cryptorchidism (25, 29) (cryptorchidism can be associated with either hypogonadotropic hypogonadism or hypergonadotropic hypogonadism). Micropenis is defined as a morphologically normal penis, with a penile urethra, the stretched length of which measured along the dorsal surface from pubis to tip of glans is more than -2.5 SD below the mean value for age: the mean value at birth is 3.5 ± 0.4 cm (SD). A stretched penile length of less than 2.5 cm in term infants is by definition a micropenis (see Ref. 25).

There are many causes of micropenis including hypogonadotropic hypogonadism, primary hypogonadism (hypergonadotropic forms), genetic defects in the LH receptor, testosterone biosynthesis or androgen action (these latter causes represent less severe mutations and loss of function than the severe or more complete forms of these genetically determined disorders), and structural anomalies, mainly developmental field defects (25).

The focus of this discussion is on hypogonadotropic hypogonadism in the male infant.

When presented with an infant with micropenis with or without cryptorchidism, it is essential to determine promptly whether the cause is isolated hypogonadotropic hypogonadism or hypogonadotropic hypogonadism associated with other pituitary hormone deficiencies (neonatal or congenital hypopituitarism). If the latter is associated with GH deficiency and/or ACTH deficiency as it commonly is, the infant is at high risk for death due to hypoglycemia or cortisol deficiency (29–31). Recurrent, severe, and persistent hypoglycemia and its manifestations (apneic spells, seizures, jitteriness, flaccidity, and temperature instability) may be due to either GH or ACTH deficiency or both deficiencies. Neonatal hypoglycemia occurred in virtually all [31 of 34 with congenital hypopituitarism (1) and 16 of 44 with septooptic dysplasia] full-term infants with neonatal hypopituitarism in our clinic.

A prompt diagnosis is critical to reduce morbidity and mortality and is greatly facilitated by the ready availability of determinations of plasma thyroxine or free thyroxine; plasma cortisol, serum electrolytes (and careful measurement of fluid intake and output to alert the physician to diabetes insipidus); serum-conjugated bilirubin; and, of course, plasma glucose. Simultaneously, a blood sample should be obtained for plasma GH, IGF binding protein-3 (32, 33), TSH, ACTH, prolactin (PRL), FSH, LH, testosterone, and inhibin B or AMH/MIS. The concentration of plasma PRL in the infant can distinguish between defects involving the hypothalamus from those at the level of the pituitary, *e.g.* pituitary aplasia or hypoplasia, Prophet of Pit-1 (PROP1), PIT1, or LIM class of homeodomain protein-3 (LHX3) mutations. Plasma PRL is high (~150 ng/dl) in umbilical vein blood of normal newborns and remains relatively high for 2–3 months after birth. In infants with hypothalamic hypopituitarism (including anencephaly) in whom the normally inhibitory hypothalamic dopaminergic system is disrupted, plasma PRL is abnormally elevated and hyperresponsive to the iv administration of TRH. In contrast, in those primary pituitary abnormalities noted above, circulating PRL is low (1, 3, 29). In addition, the diagnosis is strongly supported by the presence of prolonged conjugated hyperbilirubinemia (29, 30, 34) owing to cholestasis and giant cell hepatitis (35); pendular nystagmus; breech delivery, especially in the male fetus, is more prevalent in hypothalamic hypopituitarism [but not in pituitary aplasia (36)]; perinatal hypoxia-ischemia; optic nerve hypoplasia; midline facial malformations such as cleft lip and/or palate; facial asymmetry; and evidence of excessive urination and dehydration consistent with central diabetes insipidus. In affected males, micropenis, a frequent clinical marker, facilitates the diagnosis. Growth retardation usually is not a major clinical feature for the first 2 months of life (31, 37, 38). Notably, congenital hypopituitarism when associated with fetal ACTH deficiency is a cause of low maternal serum and urine estriol values (39).

The infantile GnRH-gonadotropin spurt affords the clinician the opportunity to nail down the diagnosis of hypogonadotropic hypogonadism by using this brief window (see bulleted list on first page) of normally increased FSH, LH, testosterone, and inhibin B values to make the diagnosis. By establishing the diagnosis of hypogonadotropic hypogonadism in the male infant, the timing of hormone replacement therapy at the age of puberty can be optimized and the uncertainties and delay in making a definitive diagnosis avoided. This stands in sharp contrast to the possibility of a delay in final diagnosis of hypogonadotropic hypogonadism until the age of 20 yr, *i.e.*, if the window of opportunity in infancy is missed.

The diagnosis of isolated hypogonadotropic hypogonadism in the male newborn (after excluding congenital hypopituitarism) raised by the presence of micropenis (with or without cryptorchidism) is supported by detecting low levels of plasma LH, FSH, testosterone, and inhibin B as well as the absence of, or very low, amplitude LH pulses. Furthermore, the iv administration of GnRH either fails to elicit an augmented LH response or results in a blunted rise in plasma LH (1, 3, 4, 29).

Cranial magnetic resonance imaging, with special attention to the hypothalamic pituitary region, is exceedingly useful for identifying the pituitary stalk dysplasia syndrome with or without an ectopic neurohypophysis or a posterior pituitary bright spot (absent in central diabetes insipidus), septooptic dysplasia and other midline defects, optic nerve hypoplasia, holoprosencephaly, and pituitary aplasia (reviewed in Refs. 1, 40–44). With special coronal sections, the olfactory bulbs and sulci can be assessed to obtain evidence of aplasia or hypoplasia of the olfactory bulbs and sulci in infants and boys with isolated hypogonadotropic hypogonadism in whom Kallmann syndrome should be considered (45).

Genetic defects and hypogonadotropic hypogonadism in the infant

The detection of single-gene mutations that result in hypogonadotropic hypogonadism in the human being and mouse and the development of genetically engineered animal models have provided useful clinical insights and diagnostic applications and have given us extraordinary insight into the complexity of the developmental and molecular biology of the hypothalamus and pituitary gland (Table 1).

One must emphasize the importance of obtaining a detailed family history, including inquiring about evidence of consanguinity, congenital malformations, delayed puberty, impaired olfaction, affected siblings, and relatives.

Our current knowledge of the genetics of hypogonadotropic hypogonadism can be conveniently separated into mutations associated with multiple pituitary hormone deficiencies, including gonadotropin deficiency (*e.g.* PROP1, HESX1, LHX3, PHF6) and isolated hypogonadotropic hypogonadism [*e.g.* KAL1, FGFR1 (KAL2), GNHR, GPR54 (KiSS1-

TABLE 1. Molecular basis for development disorders associated with micropenis due to hypogonadotropic hypogonadism

Multiple pituitary hormone deficiencies		
Gene	Hormone deficiencies	Complex phenotype
PROP1 (POU1F1)	Autosomal recessive GH, PRL, TSH, and LH/FSH (less commonly later onset ACTH deficiency) (49)	
HESX1 (RPX)	Autosomal recessive; and heterozygous mutations Multiple pituitary including diabetes insipidus but LH/FSH uncommon (50, 51)	Septooptic dysplasia
LHX3	Autosomal recessive GH, PRL, TSH, FSH/LH (52)	Rigid cervical spine
PHF6	X-linked; GH, TSH, ACTH, LH/FSH (53)	Borjeson-Lehmann syndrome: mental retardation; facies
Isolated hypogonadotropic hypogonadism		
Gene		Phenotype
KAL1		X-linked Kallmann syndrome anosmia/hyposmia, renal agenesis (54–56)
FGFR1 (fibroblast growth factor receptor)		Autosomal dominant Kallmann syndrome Anosmia/hyposmia, cleft lip/palate (57, 58)
KAL2		
GNRHR (GnRH receptor; G protein-coupled receptor)		Autosomal recessive (59–62)
GPR54 (KiSS1-derived peptide receptor GPR54)		Autosomal recessive (63, 64)
SNRPN (small nuclear ribonucleoprotein polypeptide SmN) Lack of function of paternal 15q11–q13 region or maternal uniparental disomy		Prader-Willi syndrome Obesity (65–68)
LEP (leptin)		Autosomal recessive Obesity (69–71)
LEPR (leptin receptor)		Autosomal recessive Obesity (72)
DAX1		X-linked recessive Adrenal hypoplasia (73–75)

HESX1, Homeobox gene expressed in ES cells; PHF6, plant homeo domain-like finger gene; FGFR1, fibroblast growth factor receptor 1; GNRHR, GnRH receptor; SNRPN, small nuclear ribonucleoprotein polypeptide SmN; LEP, leptin; LEPR, leptin receptor; DAX1, dosage-sensitive sex reversal-adrenal hyperplasia congenita critical region on the X chromosome, gene 1; PROP1, prophet of Pit-1; LHX3, lim homeobox gene 3.

derived peptide receptor), SNRPN (Prader-Willi), LEP, LEPR, DAX1] that can be associated with micropenis and evidence of hypogonadotropic hypogonadism in the male infant (Table 1).

Management and treatment

In infants with neonatal (congenital) hypopituitarism, after testing for pituitary hormone deficiencies, appropriate hormonal replacement therapy is initiated expeditiously (1, 29, 30, 40).

Infants with micropenis, whether owing to congenital hypopituitarism or isolated hypothalamic hypogonadism, require testosterone therapy to increase the length of the penis. Testosterone can be administered im, locally by a testosterone lotion, salve, or gel, transdermally by a testosterone patch or suppository.

We prefer to administer a long-acting testosterone ester (*e.g.* testosterone enanthate) im 25 mg every 4 wk for three doses. If a satisfactory increase in penile length (>0.9 cm) has not occurred by the end of the third month, another three-injection course can be given (25, 46). We have not found it necessary to repeat the treatment during infancy in hypogonadotropic hypogonadism. Intramuscular long-acting testosterone ester preparations provide a convenient, safe, reliable approach; compliance has been excellent.

Some clinicians have used injections of hCG; this approach requires more injections and is more costly. The penile growth 5 d after a 3-d course has been used mainly to assess androgen responsiveness.

Dihydrotestosterone preparations, either parenteral or local, have been used by some, but this steroid is not readily available, and it is more expensive. Because we are not dealing here with infants with 5α-reductase-2 deficiency, dihydrotestosterone therapy is unnecessary.

It has been proposed that male infants with hypothalamic hypogonadism be given a course of recombinant human FSH and human LH (16). Even though FSH treatment can increase testicular size, presumably by increasing the number of Sertoli cells (as also reflected in an increase in plasma inhibin B levels), we lack evidence of the importance of this approach in ensuring future fertility. Recombinant human LH with its short half-life is less effective than hCG.

In summary, the detection of congenital hypopituitarism in the male or female neonate and infant and appropriate hormone replacement therapy reduces the risk of morbidity (29), especially involving the central nervous system (47) with consequent cognitive and neurodevelopmental disabilities, as well as the liver (35), can reduce mortality dramatically and ensure normal growth (48). In the affected male infant, the presence of micropenis is an important clinical

sign of possible hypogonadotropic hypogonadism, either isolated or associated with multiple pituitary hormone deficiencies. Furthermore, the recognition of the cause of the micropenis, the normalization of penile size evoked by testosterone therapy in infancy, and the favorable prognosis for pubertal development and fertility with hormonal treatment are sources of relief and reassurance for the parents. Establishing the diagnosis of hypogonadotropic hypogonadism in the male infant greatly facilitates the initiation of hormone replacement therapy at the usual age of onset of puberty

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